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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/811,492	03/19/2004	Shannon Marshall	34098/US/2	1818

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EXAMINER

XIE, XIAOZHEN

ART UNIT	PAPER NUMBER
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1646

DATE MAILED: 09/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/811,492

Applicant(s)

MARSHALL, SHANNON

Examiner

Xiaozhen Xie

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 July 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) 5, 7, 10 and 11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6, 8 and 9 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 02 December 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

Applicant's amendments of the specification and the drawings filed 2 December 2004 have been entered. Applicant's amendment of the claims filed 20 July 2006 is acknowledged.

Election/Restrictions

Applicant's election of Group I, claims 1-9, without traverse, and species election of IFNb, in the response received 20 July 2006 is acknowledged.

Claims 1-11 are pending. Claims 5, 7, 10 and 11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-4, 6, 8 and 9 are under examination to the extent they read on the elected species.

Specification

The disclosure is objected to because of the following informalities:

The paragraph [045] is missing a number after USSN_____.

Correction is required.

Claim Objections

Claim 3 is objected to because of the following informalities: claim 3 recites non-elected inventions. Appropriate correction is required.

Claim Rejections - 35 USC § 112

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 8 and 9 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a composition comprising a prodrug agent comprising:

a) a protein that induces unwanted side effects due to undesired activity at or close to the site of administration; b) a substantially non-immunogenic polymer; c) a covalent labile linker between said protein and said polymer. The claims are broad in that the recitation of "a protein" encompasses a genus of molecules, known or unknown, with a diverse range of structures and functions. What applicant has described in the specification are polymer-conjugated therapeutic proteins, such as thrombopoietin (TPO), BMP-7, IFN- β and ciliary neurotrophic factor (CNTF). Applicant has not described the genus of polymer-conjugated proteins that can be used as prodrug. There is no teaching regarding the relationship of structure to function, such as what structure feature these molecules have. Further, there is no requirement that these molecules have any particular function. Thus, the claims encompass a genus of molecules, which vary substantially in composition, and could have very different structural and functional characteristics from the conjugation products that Applicant has disclosed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making of the claimed product, or any combination thereof. In this case, there is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of peptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that is part of the invention and reference to a method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only polymer-conjugated therapeutic proteins including TPO, BMP-7, IFN- β and CNTF, but not the full scope of the claimed conjugation products, is adequately described in the disclosure.

Claims 1-4, 6, 8 and 9 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a prodrug agent comprising a PEG-conjugated IFN- β , does not reasonably provide enablement for a prodrug comprising any polymer-conjugated protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are broad in that they encompass a prodrug comprising any protein conjugated to a polymer through a covalent labile linker. The specification defines "protein" as a molecule comprising at least two covalently attaches amino acids, which includes proteins, polypeptides, oligopeptides and peptides [020]. Thus, the recitation of "a protein" encompasses a genus of molecules, known or unknown, with a diverse range of structures and functions. The specification discloses a PEG-conjugation IFN β . The specification, however, does not provide any guidance for making or using other prodrugs comprising any protein conjugated to a polymer through a covalent labile linker. There is no teaching regarding the relationship of structure to function, such as

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what structure feature these molecules have. Further, there is no requirement that these molecules have any particular function, such as what disease these molecules can be employed in treating. While the prior art (El Tayar et al., WO 99/55377) describes the same molecules, it fails to provide compensatory guidance. Further, not all of the therapeutic proteins can be chemically modified to achieve the benefits such as enhanced plasma half-life, reduced toxicity, and increased drug stability and solubility. For example, Kozlowski et al. (Biodrugs, 2001, 15(7):419-429) state that "unfortunately, insufficient knowledge of protein structure or the inability to selectively place the PEG moiety may hinder attempts to eliminate protein immunogenicity (pp. 420, right column, 1st paragraph). Since the claims encompass a large genus of molecules with no requirement for structure and activity, and the specification does not define what these molecules will be, one of skill in the art would evaluate all non-exemplified polymer-conjugated proteins for therapeutic uses. Thus, undue experimentation would be required for the artisan to make and use the invention as broadly claimed.

Due to the large quantity of experimentation necessary to generate the nearly infinite number of polymer-conjugated proteins recited in the claims and screen same for therapeutic uses, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide therapeutic uses, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of protein structure on function, and the breadth of the claims which fails to recite any structural

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and functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite “a substantially non-immunogenic polymer” or “said polymer substantially interferes with the activity of said protein”. The phrase “substantially” is held to be indefinite because the specification lacks some standard for measuring the degree intended.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 8 and 9 rejected under 35 U.S.C. 102(b) as being anticipated by El Tayar et al. (WO 99/55377, publication date 4 November 1999). WO 99/55377 teaches PEG-IFN- β conjugates, where a PEG moiety is covalently bound to Cys¹⁷ of human

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IFN- β . WO 99/55377 teaches a pharmaceutical composition comprising the PEG-IFN- β conjugates for treating infections, tumor and autoimmune and inflammatory diseases (pp. 11 line 32 to pp. 12, line 8). WO 99/55377 teaches that IFN- β has antiviral activity and can also stimulate natural killer cells against neoplastic cells (pp. 1, lines 17-19). WO 99/55377 also teaches that IFN- β and the PEG-IFN- β conjugates are capable of inducing cellular proliferation or differentiation (see Example 3). Therefore, WO 99/55377 anticipates the instant claims.

Conclusion

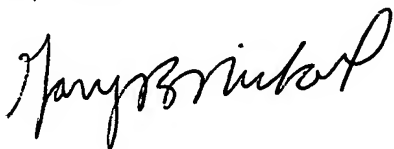
NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph. D.
August 30, 2006



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